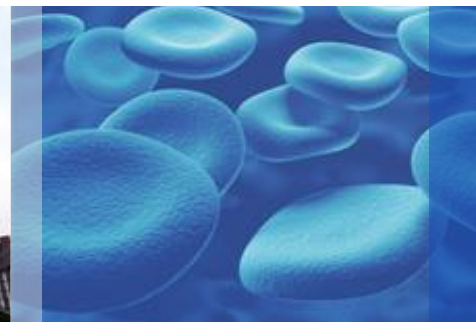


Newborn Screening for Pompe Disease: Summary of the Condition Review Workgroup Report

Alex R. Kemper, MD, MPH, MS

May 17, 2013





Condition Review Workgroup (CRW)

CRW Members	Role	Institution
Alex R. Kemper, MD, MPH, MS	Chair	Duke University
Anne M. Comeau, PhD	State NBS Public Health Program	New England NBS Program, University of Mass Medical School
Aaron Goldenberg, PhD, MPH	NBS Bioethicist	Center for Genetic Research Ethics & Law, Case Western University
Nancy S. Green, MD	Nomination & Prioritization Workgroup Liaison	Department of Pediatrics, Columbia University Medical Center
Jelili Ojodu, MPH	Public Health Impact Task Leader	NBS & Genetics, Association of Public Health Laboratories
Lisa Prosser, PhD	Decision Analysis Leader, NBS Health Economist	Health Management & Policy/ SPH; Pediatrics/Univ of Michigan Med School
Susan Tanksley, PhD	State NBS Public Health Program	Newborn Screening Laboratory TX Department of State Health Services
Stephanie Weinreich, PhD	Member	VU University Medical Center, Amsterdam, The Netherlands
K.K. Lam, PhD	Project Leader	Duke University

We also acknowledge the expert input and efforts of Scott Grosse, PhD.



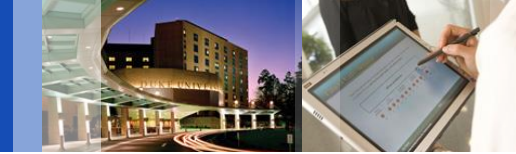
Condition Review of Newborn Screening for Pompe Disease

- Key findings from the systematic evidence review
- Projected population-level benefit based on findings from the systematic evidence review and decision analysis
- Summary of current capacity of state newborn screening programs to offer comprehensive screening for Pompe disease



Pompe Disease

- Deficiency of acid α -glucosidase (GAA), which leads to the accumulation of lysosomal glycogen
- Autosomal recessive disorder
- More than 300 mutations have been described
- Broad spectrum of illness



Classification of Pompe Disease

Infantile: Most severe

- *Onset ≤ 12 months of age*
 - **Infantile Onset *with* Cardiomyopathy** (“Classic Form”) – progressive hypotonia and cardiomyopathy; without treatment, death usually within the first year of life
 - **Infantile Onset *without* Cardiomyopathy** (“Nonclassic Form”) – typically no cardiomyopathy; longer survival, but without treatment, death in early childhood

Late-onset: Variable Presentation

- *Clinical onset > 12 months of age*
- *Most seek care for symptom onset in adulthood (> 18 years)*
- *Diagnosis ~ 8 -10 years later, and death ~ 27 years later*
- *May have mild weakness in childhood that can go unrecognized*
- *Slowly progressive myopathy*
- *Variable long-term outcomes without treatment (e.g., wheelchair dependence; ventilator assistance; respiratory failure)*



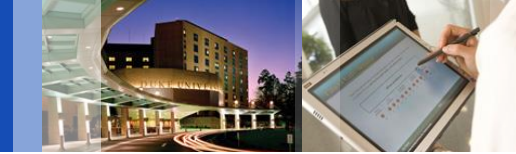
Factors that Affect Detection

Carriers

- *May have below normal GAA enzyme activity level and be identified through screening*

Pseudodeficiency

- *Low measured GAA enzyme activity level, but does not lead to Pompe disease*
- *High frequency in East Asian populations (3.9%)*
- *Can be identified by genotyping*



Factors that Affect Treatment Response

CRIM+ vs. CRIM-

- *Cross-Reacting Immunologic material – individuals make some endogenous enzyme, which may or may not be functional*
- *CRIM- can develop high titers of antibodies that neutralize ERT, leading to poor outcome*
- *Standard CRIM status detection: Western blot, however mutation analysis is usually helpful*
- *CRIM+: ~25% of CRIM+ individuals can also develop antibodies to ERT, usually not as significant as antibody development among those who are CRIM-*



Newborn Screening

- GAA enzyme activity measured in dried-blood spots
- Current methods:
 - *Fluorometric assay*
 - *Tandem mass spectrometry (MS/MS)*
 - *Digital microfluidics*
- All available screening tests effectively measure enzyme activity
- No data about whether any particular screening test would operate better in a high-throughput setting



Diagnosis

- Establish low functional GAA enzyme levels
- Genotyping
 - *Rule out pseudodeficiency*
 - *Identify carriers*
 - *Predict infantile-onset vs. late-onset*
 - *Predict CRIM status*
- By report, genotyping can be completed in ~2 days

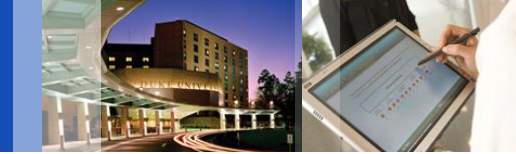


Enzyme Replacement Therapy (ERT)

Treatment: Replace alglucosidase alfa (GAA) deficiency

FDA Approval	Pompe Disease Form (Indication)	Drug	Wholesale Acquisition Cost per 50mg vial
2006	Infantile-onset (ERT start ≤ 3.5 years)	Myozyme	\$975
2010	Late-onset (≥ 8 years)	Lumizyme	\$725

- *Not curative*
- *Infusion typically every two weeks with central line*
- *Typical dose is 20 mg/kg infused over 2 hours*
- *Adverse Effects: Infusion Associated Reactions, Antibody Formation*



Systematic Evidence Review

- Guided by key questions
- Technical Expert Panel input
- 73 reports included
- Key Informant interviews



Newborn Screening for Pompe Disease TEP: Members & Conference Participation

EXPERT PANEL MEMBERS	TEP 1 July 10, 2012	TEP 2 July 25, 2012	TEP 3 (Dec Anal) Dec 6, 2012	TEP 4 (Dec Anal) Jan 8, 2013	TEP 5 (Dec Anal) Apr 25, 2013
Olaf Bodamer, MD, PhD[†]	✓			✓	✓
Barry Byrne, MD, PhD		✓	✓		
Sharon Kardia, PhD	✓		✓		
Priya Kishnani, MD, MBBS^{†, ±}	✓	✓		✓	✓
C. Ronald Scott, MD	✓			✓	✓
Muhammad Ali Pervaiz, MD		✓			
Deborah Marsden, MBBS[†]			✓		✓

[†]Served on TEP for previous 2008 review of newborn screening for Pompe disease.

[±]Nominator of Pompe disease for consideration to be added to the RUSP.



INDIVIDUAL EXPERT INTERVIEWS	DATE
Robert F. Vogt, Jr., PhD/Hui Zhou, PhD CDC/ONDIEH/NCEH – NBS Branch	17 JAN 2013
Vamsee Pamula, PhD Principal, Advanced Liquid Logic, Inc.	13 FEB 2013
Priya Kishnani, MD, MBBS[†], ± Dept of Pediatrics, Duke University Medical Center	21 FEB 2013
Joan Keutzer, PhD Genzyme Corp.	5 MAR 2013
C. Ronald Scott, MD University of Washington	6 MAR 2013
S. Rogers, MD/Patrick Hopkins/L. Smith, MD et al. Missouri NBS Program	20 MAR 2013
Khaja Basheeruddin, PhD Illinois NBS Program	27 MAR 2013
Dietrich Matern, MD, PhD Mayo Clinic – Newborn Screening Research	(18 APR 2013) ^{††}

[†]Served on TEP for previous 2008 review of newborn screening for Pompe disease.

[±]Nominator of Pompe disease for consideration to be added to the RUSP.

^{††}(Participated by written responses to questions)



Expected Epidemiology in the United States

- Overall Incidence ~1/28,000
- Infantile-onset Pompe disease
 - ~28% of cases are *infantile-onset Pompe disease*
 - ~85% of infantile cases are classic Pompe disease
 - ~75% of cases of classic infantile-onset Pompe disease are CRIM+
- Late-onset Pompe disease
 - ~72% of cases are *late-onset*
- Pseudodeficiency occurs in <1% of births



University of Washington Anonymous Dried-Blood Spot Study

- MS/MS – 111,544 samples
 - 4 were consistent with late-onset Pompe disease
 - 4 consistent with carriers
 - 3 consistent with carriers with one pseudodeficiency allele
 - 6 consistent with heterozygotes for pseudodeficiency

Estimated Results: All Pompe Disease Forms	
Overall Incidence	1 in 27,800
Overall Positive Rate	0.015%
Overall Positive Predictive Value (Based on Genotype Only)	24%



Missouri Newborn Screening Program

- Digital microfluidics - 25,971 samples (April 29, 2013)
 - 1 case with likely classic infantile-onset
 - 1 case of nonclassic infantile-onset
 - 1 case of late-onset Pompe disease
 - 2 carriers
 - 1 case of pseudodeficiency
 - 3 false positives
- As of May 15:
27,724 samples and 2 more positive screens

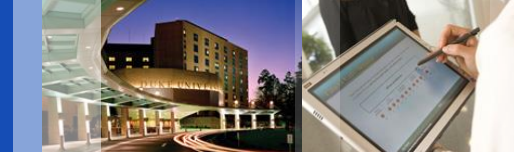
Estimated Results: All Pompe Disease Forms	
Overall Incidence	1 in 8,657
Overall Positive Rate	0.03%
Overall Positive Predictive Value	33%



Taiwan Newborn Screening Program

- Fluorescence assay – 473,738 samples
 - *9 cases of infantile-onset Pompe disease*
 - *26 cases of “later-onset” Pompe disease*
 - *Algorithm has changed over time*
 - *Using two-tiered approach all cases of infantile-onset Pompe disease and 24/26 cases of “later-onset” disease would be identified*

Estimated Results: All Pompe Disease Forms	
Overall Incidence	1 in 16,919
Overall Positive Rate	0.053%
Overall Positive Predictive Value	>90%



Newborn Screening for Pompe Disease—Summary

	Univ of Washington	Missouri NBS	Taiwan NBS
Incidence	1 in 27,800	1 in 8,657	1 in 16,919
Positive Rate	0.015%	0.03%	0.053%
Positive Predictive Value	24%	33%	>90%
Screening method	MS/MS	Digital Microfluidics	Fluorescence Assay
Total samples screened	111,544	25,971	473,738
Total True Pompe Cases	4	3	28
<i>Infantile-onset with CMP</i>	0	1	9
<i>Infantile-onset without CMP</i>	0	1	
<i>Late-onset</i>	4	1	19



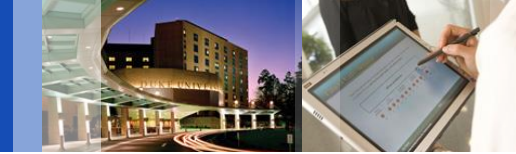
Clinical Course Before ERT Availability: Infantile-Onset Pompe Disease

	Symptom Onset <i>Median Age</i>	Diagnosis <i>Median Age</i>	Mechanical Ventilation Assistance <i>Median Age, %</i>		Death <i>Median Age</i>	% Survival [% Ventilator-Free]		
	Mos (range)	Mos (range)	Mos (range)	%	Mos (range)	12 mos	18 mos	24 mos
Infantile-onset	2.0 (0- 12)	4.7 (<0–84.2)	5.9 (0.1–39.5)	29	8.7 (0.3–73.4)	25.7 [16.9]	14.3 [8.5]	9.0 [4.9]
<i>WITH cardiomyopathy</i>	2.9	6.0						
<i>WITHOUT cardiomyopathy</i>	4.4	15.6						



Clinical Course Before ERT Availability: Late-Onset Pompe Disease

	Symptom Onset (med. consult) <i>Median Age</i>	Diagnosis <i>Median Age</i>	Death <i>Median Age</i>	Estimated Survival Post-Diagnosis (%)			
				+5 yrs	+10 yrs	+20 yrs	+30 yrs
Late-onset	28 years	38 years	+27 years post-dx	95	83	65	40



Effectiveness of ERT

- Compared to historical controls, ERT at 52 weeks (first infusion by 6 months of age)
 - *Reduced the risk of death by 95%*
 - *Reduced the risk of death or invasive ventilation by 87%*
- Overall survival at 36 months: 72%
- Overall ventilator-free survival at 36 months: 49%
- CRIM- status associated with worse outcomes
- Lower survival if ERT begun after 6 months of age



ERT Outcomes: Clinically Detected Infantile-onset Pompe disease with Cardiomyopathy

Survival by Age of First ERT (before and after 3 months of age)

	Age of First Treatment	
	ERT <3 months	ERT ≥3 months
Survival	% (95% CI)	
	(n=30)	(n=96)
12 months	92.9% (74.3 - 98.2)	90.6% (82.7 - 95.0)
24 months	81.0% (60.2 - 91.7)	72.1% (61.5 - 80.3)
36 months	76.5% (54.8 - 88.8)	61.3% (49.9 - 70.9)
Mechanical Ventilation-Free Survival		
	n=20	n=65
12 months	89.5% (64.1 - 97.3)	89.2% (78.6 - 94.6)
24 months	77.5% (50.5 - 91.0)	65.9% (52.1 - 76.7)
36 months	71.1% (43.6 - 86.9)	55.3% (40.9 - 67.5)

*DATA FROM POMPE REGISTRY, PROVIDED BY GENZYME FOR THIS REVIEW.
PLEASE DO NOT REPRODUCE WITHOUT PERMISSION.*



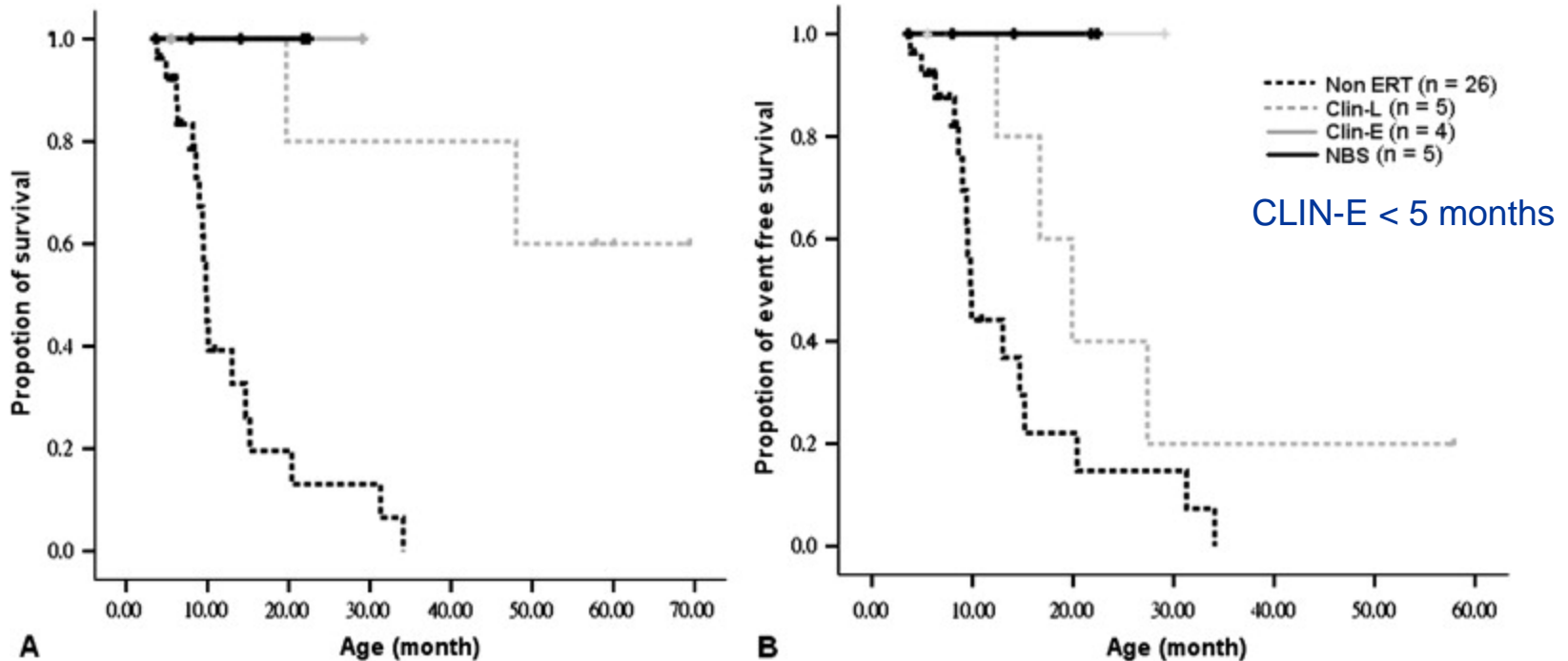
Outcomes of Early Detection of Classic Infantile-Onset Pompe Disease

- No randomized trials of screening
- From Taiwan
 - *Newborn screening leads to earlier diagnosis (median 22 days vs. 3.6 months) and improved survival*

	Detected Through Screening (%) (n=5)		Clinically Detected (%) (n=9)	
Age	Survival	Ventilator-free Survival	Survival	Ventilator-Free Survival
24 months	100	100	89	67



Outcomes of Early Detection of Classic Infantile-Onset Pompe Disease

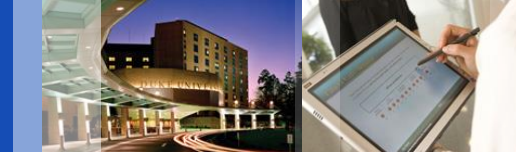


Chen L-R, Chen C-A Chiu S-N, et al. Reversal of cardiac dysfunction after enzyme replacement in patients with infantile-onset Pompe disease. *J Pediatr.* 2009;155:271-275.



Antibodies to ERT

- All CRIM- patients and ~25% of patients who are CRIM+ will develop antibodies. Antibody production in those who are CRIM- is associated with poor outcome.
- All patients who are CRIM- have classic infantile-onset disease and require ERT. Screening leads to earlier initiation of ERT.
- Immunotherapy administered in early infancy can protect against the development of neutralizing antibodies; case studies suggest that immunomodulation after the initiation of ERT is not as effective in protecting against the development of neutralizing antibodies.
- Recent report described an algorithm for immunomodulation that was tested in 7 CRIM- subjects
 - *4 have not developed antibodies (age 20 months, 21 months, 26 months, 29 months)*
 - *2 required a second course of immunomodulation (age 20 months, age 29 months)*
 - *1 died from respiratory failure (age 15 months)*



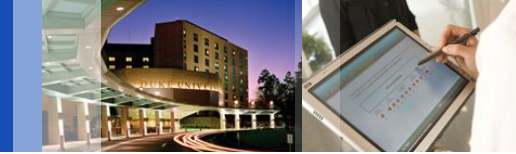
Pre-symptomatic Detection of Late-Onset Pompe Disease

- No trials of pre-symptomatic ERT for late-onset disease
- Treatment decisions based on presence of weakness or muscle damage (e.g., elevated CK). MRI can also show muscle damage.
- Recommendations for follow-up not standardized
- Potential harms of early identification include treatment with ERT, central line placement, economic cost of lifelong treatment, and psychosocial harm.
- There is evidence from an RCT of ERT for symptomatic individuals (mean age in the 40s) that ERT can improve respiratory status and motor function.



Pre-symptomatic Detection of Late-Onset Pompe Disease

- The effect of treatment begun after symptom development might be limited because muscle damage is irreversible. Treatment begun before symptom development might avoid muscle damage.
 - *Biologic plausibility for pre-symptomatic treatment*
 - Muscle damage cannot be reversed by ERT
 - Autophagic inclusion bodies persist after ERT even after reduction of glycogen in muscle cells
- Testing this hypothesis would require a prospective study that would take many years.



Symptom Development in Late-Onset Pompe Disease

- One case series from Taiwan describes six patients diagnosed through screening with “later onset” Pompe disease (asymptomatic at diagnosis)
- Of these, 4 would likely be classified as late-onset Pompe disease and began treatment
 - 14 months – *Hypotonia*
 - 34 months – *Frequent falling*
 - 36 months – *Frequent falling*
 - 7 years - *Hypotonia*



Summary

- Screening can identify newborns with ALL forms of Pompe disease.
- Pseudodeficiency is less common in the United States than East Asia.
- There is good evidence that early identification of infantile-onset Pompe compared to clinical detection improves outcomes.
- Most cases of infantile-onset Pompe disease are CRIM+.
 - *CRIM- is associated with worse outcomes*
 - *Immunomodulation appears to improve outcomes, and early immunomodulation may be more effective*
- Most cases of Pompe disease identified through newborn screening will be the late-onset form.
- There is no direct evidence that pre-symptomatic treatment leads to better outcome; however, there is biologic plausability.

Newborn Screening for Pompe Disease: Assessing Population-Level Benefits using Decision Analysis

Lisa A. Prosser, Ph.D.
UNIVERSITY OF MICHIGAN

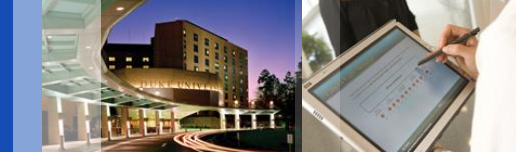
DACHDNC Meeting
May 17, 2013





Background: Decision analysis

- Validated approach for evidence synthesis
- Using simulation modeling, ranges can be estimated for population-level health benefits
- Identification of assumptions and key areas of uncertainty



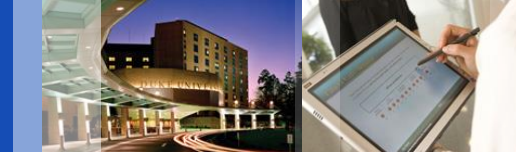
Analytic Approach

- Computer simulation model to evaluate outcomes for universal newborn screening for Pompe disease compared with clinical identification
- 3 expert panels: Dec 2012, Jan & April 2013
- Key health endpoints:
 - *# cases identified*
 - *# deaths averted*
 - *# ventilator-dependent cases averted*



Modeling Assumptions

- All identified cases of infantile-onset Pompe disease are eligible for ERT
- Key outcomes assessed for infantile-onset cases only
- Additional number of late-onset cases identified with newborn screening is unknown



Results: Infantile & Late-Onset Cases

- Assuming an annual US newborn cohort of 4 million*, newborn screening is projected to identify 134 cases, including both infantile and late-onset Pompe disease
- Of these 134 cases,
 - *40 cases are expected to be infantile-onset*
 - *94 cases are expected to be late-onset (40-70% of which may be undetected with clinical identification)*
- ~10 false negative results (late-onset only)

* not at increased risk for Pompe disease



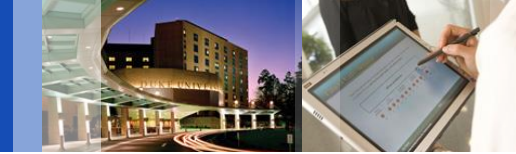
Results: Infantile-Onset Cases Identified

	NBS	Clinical Identification
Infantile onset (all)	40 (19-61)	36 (16-56)
Infantile onset with cardiomyopathy	34 (28-36)	34 (28-36)
Infantile onset without cardiomyopathy	6 (4-12)	2 (0-8)



Results: Health Outcomes

- Benefits of newborn screening:
 - Infantile-onset with cardiomyopathy:
 - Earlier identification and initiation of treatment (~22 days compared to 4-5 months of age on average)
 - Infantile-onset without cardiomyopathy:
 - Identification and treatment of 4 additional cases
- Key health outcomes, per year:
 - 13 averted deaths (range 8-19)
 - 26 additional individuals who would not require invasive ventilation (range 20-28)

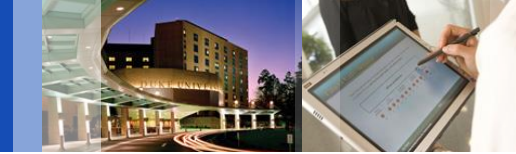


Summary

- Projected health benefits for identified cases
 - *Infantile-onset only*
 - *Increased survival*
 - *Fewer individuals with invasive ventilation*
- Benefits and harms of identifying late-onset cases is not included

Newborn Screening for Pompe Disease: Evidence Review and Public Health Impact Assessment

Jelili Ojodu, MPH
DACHDNC Meeting
May 17, 2013



Sample: 10 state public health NBS programs selected to represent the NBS public health system.

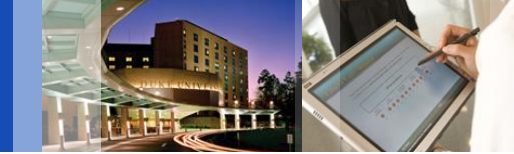
Selection Criteria

General Program Characteristics

- Many Regional Collaboratives
- Newborn population sizes
- State mandate or not to screen for RUSP conditions
- State laboratory facilities vs. outsourcing
- Second screen requirements

Condition-Specific NBS Screening Factors

- Currently screening for condition of interest or not
- Equipment on site
- Experience with NBS screening for similar conditions



Selected Sample and Program Characteristics

State	Regional Collaborative	State Mandate for RUSP?	Outsource Routine NBS Lab Testing?	Newborn Population (2010)	Academic Affiliation?	Pilot for Pompe
Massachusetts	Region 1	No	No	73,267	Yes	
Delaware	Region 2	No	No	11,682	No	
New Jersey	Region 2	Yes	No	103,932	No	
South Carolina	Region 3	No	No	55,602	No	
Illinois	Region 4	Yes	No	161,760	No	X
Minnesota	Region 4	No	No	68,269	No	
Missouri	Region 5	Yes	No	77,588	No	X
Iowa	Region 5	No	No	38,574	Yes	
Nebraska	Region 5	No	Perkin Elmer	26,242	No	
Texas	Region 6	No	No	492,768	No	
New Mexico	Region 6	Yes	Oregon	27,028	No	
Oregon	Region 7	No	No	45,899	No	
Washington	Region 7	No	No	86,507	No	X



Data Collection

Stage 1: Electronic surveys (Qualtrics) to NBS program directors between February-April, 2013 to assess readiness and feasibility to implement NBS for Pompe Disease.

Status: Completed by NBS program directors; 92% response rate.

Stage 2: Customized telephone interviews were conducted with newborn screening program directors and colleagues in April 2013.

Status: Completed; all survey responders completed interview (n=12)



Definitions

Feasibility

Do program directors believe there is:

- An established screening test?
- A clear approach to diagnostic confirmation?
- A clear approach to long-term follow-up?

Readiness

Do program directors think they have:

- All resources needed for screening, diagnostic confirmation, and long-term follow-up?
- Authorization for screening?



General Process for Adding Conditions

State(s) consider condition(s), design and execute studies, provide study data

- Condition is added to the RUSP

- State decides to add or not to add condition

6 months to 1 year

- State changes rules/statutes

6 months to 1 year

- State obtains funding

1 to 3 years

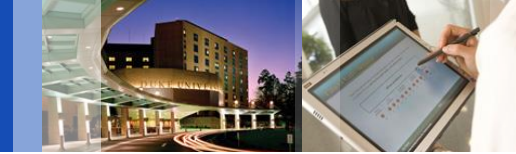
- State conducts implementation or pilot

1 to 3 years



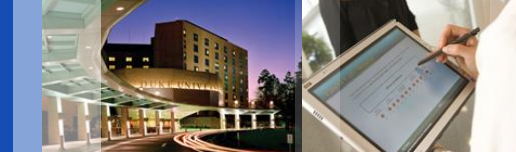
Factors for Implementation

- Authorization to screen
- Funds
- Securing a contract for equipment and reagents
- Acquiring equipment and re-organizing space
- Validating the method
- Getting QC materials
- Conversations with clinicians/specialists
- Hiring new staff
- Training laboratory and follow-up staff
- Creating educational materials
- Updating reports
- Creating protocols
- Changes to IT system



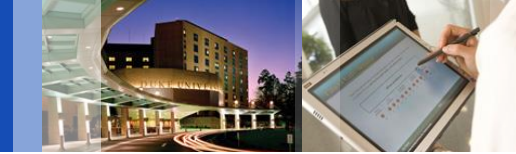
Stakeholders Involved in Adding Conditions

- NBS Advisory Committee (includes consumers)
- State Health Official/Commissioner
- Legislators
- State Board of Health
- Public Health Department



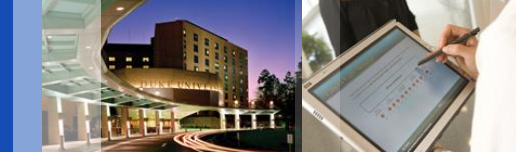
Key Findings- Feasibility

- No definitive findings as to which method would be best to use for Pompe Disease screening existed among those surveyed.
- 55% (6/11) of program directors surveyed were comfortable with the NBS program's ability to provide diagnostic confirmation for Pompe Disease, while 45% (5/11) of them were uncertain.



Key Findings- Feasibility

- 73% (8/11) of program directors surveyed were comfortable with their program's ability to provide/facilitate treatment
- 64% (7/11) of program directors surveyed were comfortable with their program's ability to conduct follow-up services for Pompe Disease screening.



Key Findings- Readiness

- 83% (n=10) of the state programs surveyed rely upon their NBS advisory committees and state health officials to assist with adding conditions to panels.
- 73% (8/11) of NBS program directors surveyed stated that they did not have adequate funding if they were required to implement screening for Pompe Disease today.



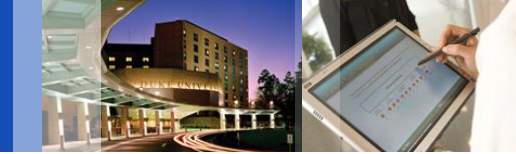
Key Findings- Readiness

- 58% (7/11) require change in state rules to add a new condition to the uniform panel.
- 42% (5/12) require legislative action to add a new condition to the uniform panel.



Key Findings- Readiness

- Staffing was listed most frequently as the greatest barrier. 73% (8/11) of program directors surveyed believed that if they were required to implement screening for Pompe Disease today, they would not have adequate staff.
- 55% (6/11) of program directors reported historical difficulties recruiting adequate staff with the necessary expertise.



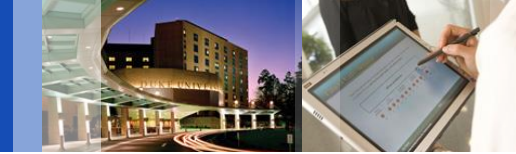
Key Findings – Readiness

- 73% (8/11) of the program directors noted that there was a shortage of metabolic specialists/those trained to handle cases of Pompe Disease.
- Short-term follow-up programs would need to develop additional protocols and educate hospitals and providers on what to do with out-of-range results.



Key Findings

- Several states have been unable to secure funding to conduct newborn screening for SCID (already on RUSP)



Summary

- NBS programs are in the process of validating different testing platforms for population-based screening for Pompe Disease.
- Uncertainty related diagnostic follow up for treatment
- Paradigm shift: NBS for a condition where most infants identified will have the late-onset form.
 - NBS cannot be performed for infantile-onset only



Questions?